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10/593,349	12/05/2006	Mitsuo Kawase	129422	7396

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EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
09/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,349	KAWASE ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

No IDS has been filed to date of the instant Office communication.

Drawings

The drawings received on September 19, 2006 are acceptable.

Specification

The specification is objected to because the specification refers to patent document which does not exist.

On page 3, of the instant specification, patent document 3 is referred to as being a "Pamphlet of International Publication No. 95/251116." It is presumed that the pamphlet is referring to a patent publication by WIPO. However, there is no such document of the publication number.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 12, line 30. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the phrase, "DNA array of any one of claim 1."

Claim 7 refers to a single DNA array, therefore, it is indefinite what is meant by "any one of" claim 1. It appears that the phrase, "any one of" should be deleted, and this interpretation has been assumed for the purpose of prosecution.

Claim 7 recites the phrase, "the first probe spot," and "the second probe spot."

Claim 1 recites the term, "first probe spots" and "second probe spots" (note plural). Therefore, it is unclear which of the spots, the singular term is referencing to.

Claim 8 is indefinite because it cannot be determined what metes and bounds are covered by the limitation, "the probe length." Claim 8 depends from claim 7 in that the probe length of the probes of the first and second probe spots are determined by the method disclosed by claim 7.

Since the length of the probe determined by claim 7 is arbitrary and varies based on the nature of the genes and polymorphisms being targeted, it cannot be determined what length is deemed to be within the metes and bounds of the DNA array of claim 8.

For the purpose of prosecution, any length would meet the limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Chee et al. (U.S. Patent No. 5,837,832, issued November 17, 1998).

In making the present rejection, the claim has been construed in that the method of producing said array bears no patentable distinction from the array of the prior art as the array

produced by claim 7, does not preclude in probes of the first and second spots having the same sequences, so long as said first and second probe spots comprise exactly complementary sequence to the first and second polymorphism pattern of the gene, respectively.

Chee et al. disclose a DNA array which comprises a first probe spot containing one or more probe for a particular polymorphism, and a second probe spot containing one or more probe for a second particular polymorphism (see Figure 2; column 6, lines 21-34), wherein probes of varying lengths are employed (column 10, lines 34-39; column 20, lines 52-55; column 21, lines 40-48).

Therefore, Chee et al. anticipate the invention as claimed.

Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Cronin et al. (WO 01/66804 A2, published September 13, 2001).

Cronin et al. provide a first set of polynucleotide probes which are immobilized on an array, wherein this initial probe set includes probes complementary to the reference sequences.

The reference sequences are disclosed as being, "specific for each sequence variation to be determined or each gene to be profiled." The target nucleic acid is disclosed as being hybridized to the array-immobilized probes, then the hybridization pattern is analyzed.

The artisans then explicitly state that a second probe set is designed wherein the hybridization performance of one or more polynucleotide probes are modified, wherein in particular, the artisans contemplate the altering of probe lengths (page 9, lines 14-28).

The artisans then disclose that the designed second set of polynucleotide probes immobilized on an array, and that this array is hybridized to the target nucleic acid. (page 9, line 34 through page 10, line 3), wherein each sequence variant of the target nucleic acid is re-estimated from the relative hybridization intensities of the probes. The artisans explicitly state that this probe

set design can be reiterated until all sequence variations of the target nucleic acid may be determined simultaneously under a single set of conditions. page 10, lines 3-8)

The artisans explicitly contemplate probe design for single nucleotide polymorphisms (page 10, lines 15-16)

The artisans state:

"Upon the redesign of the initial probe set, a second set of polynucleotide probes is immobilized on an array. The target nucleic acid is then hybridized with the second set of polynucleotide probes. Each sequence variation or gene expression is reestimated from the resulting hybridization pattern. Further cycles of array design and hybridization pattern analysis can be performed in an iterative fashion, if desired, until all sequence variations or gene expressions are determined under a single set of conditions." (page 29, lines 22-28)

The artisans state that the resulting DNA array would be specific for their polymorphisms and may have probes which are differing in lengths:

"The resulting polynucleotide probe set may have uneven nucleotide lengths, but have more balanced Tm range." (page 25, lines 31-32)

A working example of such finished product, DNA array is disclosed by Cronin et al.:

"Figure 3 compares the hybridization results using the fully optimized array for two patient samples, one that is heterozygous for the T341C polymorphism and one that is homozygous for T at that site." (page 6, lines 14-16)

"Modification made to these probes for the second array iteration included lengthening probes that did not give hybridization signal intensities greater than three times background and shortening poorly discriminating probes. Probe length for version 2 ranged from 16 to 20 nucleotides….This resulted in more probe sets giving fluorescence signals above the cutoff value after hybridization and a good heterozygote discrimination ratio." (page 36, lines 14-20)

"Two final design optimization cycle applied to the Tm selected probe design resulted in genotyping array version six which has a global homozygote discrimination ratio of 6.6 and an average heterozygote discrimination ratio of 1.0." (page 37, lines 8-11)

The DNA array of Cronin et al. anticipates the DNA array of the instant claim therefore.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. (WO 01/66804 A2, published September 13, 2001).

Cronin et al. disclose a DNA array for detecting polymorphisms in a nucleic acid sequence, and in particular, single nucleotide polymorphism (page 4, lines 32-33; page 10, lines 15-16), on a solid support (page 4, lines 10-21), said solid support comprising:

a) a first probe spots group consisting of one or more probe spots each containing one or more probes hybridizable with a polynucleotide of the gene, in which the probes are exactly complementary to the first polymorphism pattern of the gene; and

b) a second probe spots group consisting of one or more probe spots each containing one or more probes hybridizable with the polynucleotide of the gene, in which the probes are exactly complementary to the second polymorphism pattern of the gene (page 9, lines 14-28[1]; see also probe list on pages 34-36).

With regard to claim 2, the first probe spots and the second probe spots each consists of 2 to 10 probe spots.

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[1] Initial probe set includes probes complementary to the reference sequences. The reference sequences are disclosed as being, "specific for each sequence variation to be determined or each gene to be profiled." The target nucleic acid is disclosed as being hybridized to the array-immobilized probes, then the hybridization pattern is analyzed. (page 9, lines 14-28)

With regard to claims 5 and 6, the artisans disclose the method of using their array for measuring the signals from the labeled polynucleotides hybridized to the array (page, lines 14-28[2]).

With regard to claim 7, the artisans disclose that they use their array to determine an appropriate probe length for detecting single nucleotide polymorphism of a gene, in that the artisans disclose that upon analyzing the hybridization pattern of the first set of polynucleotide probes, they designed second set of polynucleotide probes immobilized on an array, and that this array is hybridized to the target nucleic acid. (page 9, line 34 through page 10, line 3), wherein each sequence variant of the target nucleic acid is re-estimated from the relative hybridization intensities of the probes.

The artisans explicitly state that this probe set design can be reiterated until all sequence variations of the target nucleic acid may be determined simultaneously under **a single set of conditions** (page 10, lines 3-8).

The artisans do not explicitly disclose that their DNA array comprises a first probe spots group and a second probe spots group, wherein the probe lengths in the probe spots is different from each other (claim 1), or that the probe spots are arranged in the order of the probe length (claim 3).

The artisans do not explicitly disclose that their DNA array should be comprised in a kit (claim 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Cronin et al., thereby arriving at the claimed invention for the following reasons.

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[2] The target nucleic acid is disclosed as being hybridized to the array-immobilized probes, then the hybridization pattern is analyzed. The artisans then explicitly state that a second probe set is designed wherein the hybridization performance

While Cronin et al. do not explicitly disclose that their DNA array comprises a first probe spots group and a second probe spots group, wherein the probe lengths in the probe spots differ from each other, and that the probe spots are arranged in the order of the probe lengths, the motivation to arrive at the claimed invention is provided for by Cronin et al.:

> "A critical step in array-based hybridization technology is finding a condition where there is sufficient discrimination between perfect matches and mismatches. One problem is that for a particular target sequence, there is only one perfect match with a polynucleotide probe, while there are many possible end and internal mismatches. Unless the discrimination is very strong, there will be an inevitable background problem contributed by a large number of end and internal mismatches. Another problem is the sequence dependence of hybridization performance. G/C base pairs form three hydrogen bonds as opposed to two hydrogen bonds between A/T base pairs. Therefore, polynucleotide probes rich in G/C pairs will form more stable hybridization complex with target nucleic acids than A/T rich polynucleotides. If a more stringent condition is chosen that allows effective discrimination between perfect matches and mismatches in G/C rich sequence, many A/T rich sequences may not form enough hybridization complex to be detected, which leads to false negatives. Alternatively, if one chooses a less stringent condition to stabilize the weak A/T rich sequences, there will not be enough discrimination against mismatches in G/C rich sequences and many false positives will result." (page 3, lines 1-16, Cronin et al.)

Cronin et al. recognizes the difficulty in finding a single condition where a plurality of probes immobilized on an array are maximized for specificity:

> "There is a need in the art for an effective and cost-saving method for modulating and optimizing hybridization performance of polynucleotide probes on an array" (page 3, lines 25-27)

> "applicable to simultaneously determining multiple sequence variations…under a single set of conditions" (page 4, lines 8-9)

In solving this need, the artisans generate a first set of probes on an array for testing the hybridization specificity and efficiency, their analysis, followed by the generation of a second set of probes which are modified based on the previous hybridization specificity and efficiency:

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of one or more polynucleotide probes are modified, wherein in particular, the artisans contemplate the altering of probe lengths (page 9, lines 14-28).

> "the method comprises the steps of: (a) obtaining an array where in a set of polynucleotide probes designed specifically for each sequence variation ... is immobilized on the array; (b) hybridizing target nucleic acid(s) to the array-immobilized polynucleotide probes under a pre-determined condition; (c) determining the difference in hybridization between target nucleic acid(s) and the array-immobilized polynucleotide probes; (d) changing the melting temperature, length, sequence composition, or hybridization environment of at least one polynucleotide probe; and (e) repeating steps (a)-(d), if necessary, until the differences n hybridization between target nucleic acid(s) and array immobilized polynucleotide probes simultaneously indicate the presence or absence of two or more sequence variations in target nucleic acid(s) ... under the pre-determined condition." (page 4, lines 10-21)

The artisans also explicitly disclose that the length of the polynucleotide probes may be changed (page 4, lines 24-25) and that, "the temperatures of polynucleotide probes immobilized on the array differ by no more than about 15, 10, or 5° C" (page 5, lines 4-5).

Cronin et al. discuss that probes of varying length would result in higher specificity:

> "A wide range of probe length may be used. Longer probes do not necessarily improve their sensitivity, because long probes usually exhibit higher Tm than that of actual assay conditions, allowing for more mismatches. Although shorter probes increase the chances of nonspecific appearance of such sequences in the target sequences, they may exhibit a much higher penalty on mismatches. Therefore one may design optimal probes based on their hybridization performance, instead of the length of the probes." (page 25, lines 17-23).

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to employ probes of varying lengths in the initial probes of Cronin et al., so as to facilitate the identification of probes which are highly specific for their variant nucleotides under a single set of assay condition.

In addition, whether or not such probes are arranged in the order of the probe length, such determination would have been well within the purview of an ordinarily skilled artisan. Arranging areas in which probes are immobilized for identification of their characteristics is also demonstrated by Cronin et al. wherein a first row of probes is identified as having a sequence variation at one

position, while the second row of the probes is identified as having a sequence variation at a position, one base over (n+1) (see Figure 2).

With regard to the limitation drawn to a kit, it would have been further *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the DNA array of Cronin et al. into a kit in view of the conventionality of kits in the analytical arts for the advantages of convenience, cost-effectiveness, matched and/or preweighed components, etc.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
9/20/2008

/YJK/